

## REMARKS

### I. Status Summary

Claims 1-27, 46-53, 60-74, 76, and 77 are pending and have been examined. The following rejections have been presented in a Final Official Action dated June 6, 2007.

Claims 1-10 and 60 have been rejected under 35 U.S.C. § 102(a) upon the contention that the claims are anticipated by Howard et al. (2000) 11 *Mammalian Genome* 234-237 (hereinafter "Howard").

Claims 1-10, 15, 19-27, 46-53, 64-74, 76, and 77 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl et al. (1997) *Proc Natl Acad Sci USA* 94:5231-5236 (hereinafter "Diehl").

Claims 11-14, 16-18, and 61-63 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans et al. (1986) *J. Immunol* 137:2355-2360 (hereinafter "Dindzans"), and further in view of Hedrich (1981) *Genetic Monitoring*, Volume 1, Chapter 8 (hereinafter "Hedrich").

Claims 2 and 47 have been canceled without prejudice.

Claims 1, 8, 10, 11, 15, and 46 have been amended. The amendments to claims 1 and 46 result from incorporating the elements of currently pending claims 2 and 47, respectively, into the claims. The amendments to claims 8, 10, 11, and 15 are limited to updating the dependency of these claims to depend from claim 1 rather than canceled claim 2. As such, support for the amendments can be found in the claims as originally filed. Accordingly, no new matter has been added as a result of the claim amendments.

Reconsideration of the application based on the amendments and remarks set forth below is respectfully requested.

### II. Summary of the September 18, 2007 Telephone Interview

On September 18, 2007, a telephone interview was held between applicants' representatives Arles A. Taylor, Jr. and Christopher P. Perkins and Examiners Forman and Shaw of the United States Patent and Trademark Office (hereinafter "the Patent Office"). During the telephone interview, certain terms appearing in the claims were discussed. The references cited by the Patent Office were also discussed

Also discussed was how the renewable populations of genetically diverse individuals were distinguishable from the populations disclosed in the cited references. In particular, applicants' representatives pointed out how the backcrossing and intercrossing disclosed in certain of the cited references did not relate to backcrossing or intercrossing recombinant inbred (RI) individuals, but instead referred to conventional, known backcross and intercross mapping strategies. The Patent Office requested that documentary evidence of how these conventional mapping strategies are typically performed be included in the instant amendment. **Exhibit C (Exhibits A and B** having been filed along with Amendment B dated December 5, 2003) is being submitted herewith in response to this request.

And finally, the nature of the exemplary renewable populations of genetically diverse individuals recited in, for example, claims 2 and 47, was also discussed. The Patent Office indicated that with respect to the populations recited in claims 2 and 47, these populations appeared to be distinguished over the populations disclosed in the cited references provided that the nature of intercross and backcross mapping could be clarified. The Patent Office further suggested that incorporating the elements of claim 2 into claim 1 and into other independent claims as appropriate could lead to allowance of these claims.

Applicants would like to thank Examiners Forman and Shaw for their time and efforts in discussing the instant subject matter during the September 18, 2007 telephone interview. Applicants respectfully submit that the amendments and remarks presented herein are believed to be consistent with the discussions of the telephone interview.

III. Initial Comments with Respect to the Patent Office's Assertions  
Presented in the Response to Arguments

Initially, applicants wish to address certain assertions presented by the Patent Office in the "Response to Arguments" section of the June 2007 Final Official Action. Particularly, applicants wish to point out additional support for the interpretations of certain claims elements that applicants have advanced in the instant prosecution.

First, the Patent Office asserts that it does not appear that the specification supports the definition of the term “renewable population” applicants provided in the previous Amendment. Applicants had pointed to page 18 of the instant specification, which states “the phrase ‘renewable population of genetically diverse individuals’ refers to a population that can be faithfully regenerated and comprises a limited repertoire of possible genotypes, although individuals within the population are genetically diverse” (emphases added). According to the Patent Office, the term “regenerated” in this definition is not limited to reproducing identical genomes, and thus any natural population capable of producing offspring would be considered renewable.

Applicants respectfully disagree. Applicants respectfully submit that the phrase “faithfully regenerated” implies more than just that another population of the same species can be created. Applicants respectfully submit that being able to faithfully regenerate a population implies that the members can be regenerated, not simply replaced. Support for this interpretation can be found in the instant specification at page 4, line 32, through page 5, line 3, which states: “Natural populations encompass individuals that are genetically diverse and each genotype is unique. However, environmental effects cannot be efficiently controlled since the unique genotypes cannot be reproduced by natural or assisted mating” (emphasis added). The specification further discloses that “[o]ptimally, the environmental noise should approach zero for maximum sensitivity of gene mapping” (see page 15, lines 8-9). Additionally, page 2, line 31, through page 3, line 2, of the instant specification states that “[e]xisting strategies for gene mapping generally rely on large sample sizes that achieve low genetic noise or renewable inbred populations that achieve low environmental noise, but not both” (emphasis added). And finally, page 14, lines 19-22, state that “[t]he power of detection [of a genetic locus] is correlated with target gene strength, and is optimal when genetic noise and environmental noise in the mapping population is low. Conversely, the power of detection is diminished by genetic noise and environmental noise” (emphases added).

Thus, applicants respectfully submit that when viewed in its entirety, the instant specification discloses that ideal genetic mapping populations minimize the effects of both genetic and environmental noise. Since natural populations poorly control

environmental effects, applicants respectfully submit that the specification as filed clearly indicates that the mapping populations of the presently disclosed subject matter do not include natural populations. As such, applicants respectfully submit that the Patent Office's interpretation of the phrase "renewable population" as including a natural population is inconsistent with the specification, and thus is believed to be improper.

Applicants also respectfully disagree with the Patent Office's assertion on page 10 of the June 2007 Final Official Action that a natural population (*i.e.*, an offspring population) would comprise a limited repertoire of possible genotypes that were present in the parental population. Applicants respectfully submit that this assertion is based on an incorrect interpretation of the term "genotype". Applicants respectfully submit that an individual's "genotype" is his or her entire genetic complement. Thus, while it may be accurate to say that a natural population generated by breeding a parental population could comprise all of the possible alleles that are present in the parental population, the alleles would be present in the natural population in different combinations than they were present in the parental population, and thus the members of the offspring population would have different genotypes from the members of the parental population.

Stated another way, applicants respectfully submit that it is not accurate that a natural population would comprise a limited repertoire of possible genotypes that were present in the parental population. Since meiotic recombination in the parental population would rearrange the haploid genomes that would be transferred to the natural (offspring) population, a member of a parental population could not pass on its identical genotype by natural or assisted breeding unless it was homozygous at every locus and thus meiotic recombination did not rearrange its genome. Thus, and as applicants have argued, parental populations cannot regenerate natural (offspring) populations even if the same parental individuals are bred to each other repeatedly. Meiotic recombination ensures that the offspring population comprises unique genotypes from those found in the parental population in every instance.

Summarily, applicants respectfully submit that the Patent Office's definition of the term "genotype" is inaccurate in that it does not consider the individuals entire genotype, and thus its assertion that a natural population can be "renewed" and/or "faithfully regenerated" is believed to be inconsistent with how one of ordinary skill in the art would

interpret these terms in light of the instant specification. Given that the Patent Office must interpret claim terms from the perspective of one of ordinary skill in the art and in light of the specification according to M.P.E.P. § 2111, applicants respectfully submit that Patent Office's "broadest reasonable interpretation" of the phrase "renewable population" is believed to be improper as it conflicts with the instant specification.

#### IV. Responses to the Anticipation Rejections

Claims 1-10 and 60 have been rejected under 35 U.S.C. § 102(a) upon the contention that the claims are anticipated by Howard. Claims 1-10, 15, 19-27, 46-53, 64-74, 76, and 77 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and present the following remarks.

##### IV.A. The Rejection Over Howard

According to the Patent Office, Howard teaches a method comprising (a) providing a renewable population of genetically diverse individuals; and (b) mapping the genomes of individuals within the renewable population of genetically diverse individuals that display the phenotype, whereby a genetic locus that modulates the phenotype is identified. More particularly, the Patent Office asserts that Howard teaches that the recombinant inbred lines AXB and BXA (which are both homozygous) were both used to study a mouse mutation that causes altered mammary gland development. The Patent Office further asserts that backcross and intercross progeny of the AXB and the BXA lines display the phenotype of interest. And finally, the Patent Office asserts that Howard teaches that they are now mapping the *ska* gene in the AXB/BXA recombinant inbred strains of mice and in the back cross and intercross panels in order to make a high resolution map to isolate the *ska* locus.

Applicants respectfully submit that in the context of the terms "backcross and intercross" as found in Howard, the "AXB" and "BXA" symbols used do not correspond to backcrosses or intercrosses of RI individuals, and as such, does not anticipate the instant claims. Applicants further respectfully submit that Howard's "backcross and

intercross panels” that are disclosed as being used for making a high resolution map to isolate the *ska* locus also do not refer to backcrosses and intercrosses of the AXB and BXA RI lines.

To elaborate, applicants respectfully submit that Howard discloses the following:

Crosses of AXB and BXA resulted in a total of 115 F<sub>1</sub> progeny (Table 1). All F<sub>1</sub> mice have 10 nipples in the correct position, which suggests that the *ska* mammary gland patterning trait is not dominant or semi-dominant. Backcross and intercross mice display both alterations in the number and placement of nipples like those observed in the A/J strain (Fig. 2). Approximately 25% of both the AXB and BXA intercrosses and approximately 50% of the female backcross mice observed display the *ska* mutant phenotype (Tables 2, 3). Analysis of these data is consistent with the *ska* mutation being caused by a single autosomal recessive locus.

Howard at page 235, left column paragraph 1.

Applicants respectfully submit that the phrase “[c]rosses of AXB and BXA resulted in a total of 115 F<sub>1</sub> progeny” (emphasis added) indicates that the AXB and BXA animals were F<sub>1</sub> animals produced by crossing a female A/J mouse with a male C57BL/6 mouse (AXB) or a female C57BL/6 mouse with a male A/J mouse (BXA), respectively. This is set forth in Table 1, which states “outcross females (AXB F<sub>1</sub>) and (BXA F<sub>1</sub>) were observed as pups while lactating” (see notes associated with Table 1 on page 235 of Howard; emphasis added). The term “outcross” would be understood by one of ordinary skill in the art to refer to a mating of individuals that are genetically unrelated, which individuals in different AXB or BXA RI lines are not since they have received genetic information from the same (ultimate) grandparents (e.g., A/J or C57BL/6). Accordingly, applicants respectfully submit that it appears that the use of the AXB and BXA nomenclature in Howard does not in this case refer to RI individuals but to F<sub>1</sub> individuals.

Furthermore, applicants respectfully submit that these F<sub>1</sub> individuals are the individuals that are employed in Howard in the disclosed backcross and intercross mapping strategies. Applicants respectfully submit that backcross and intercross mapping strategies are standard techniques known to one of ordinary skill in the art. In fact, applicants respectfully submit that these strategies and the drawbacks associated therewith are discussed in the instant specification at page 3, lines 4-19.

These techniques are also summarized on pages 233-235 of Silver (1995) Mouse Genetics: Concepts and Applications, Oxford University Press, New York, New York. A true and accurate photocopy of these pages is submitted herewith as **Exhibit C**. As described in **Exhibit C**, a backcross mapping protocol involves an outcross of two strains (in Howard, strains A and B are A/J and C57BL/6) followed by a cross of  $F_1$  progeny back to a member of one of its parental strains (*i.e.*, the “backcross”). This is depicted in Figure 9.11 included in **Exhibit C**. Similarly, Figure 9.12 of **Exhibit C** depicts a typical intercross strategy, in which the same  $F_1$  animals generated in step 1 of the backcross strategy are intercrossed (*i.e.*,  $F_1 \times F_1$ ) instead of being backcrossed.

Turning now to Howard, it is noted that as per the discussion hereinabove,  $F_1$  mice are produced by reciprocal matings of A/J and C57BL/6, which means that  $F_1$  progeny are generated by mating female A/J mice to male C57BL/6 mice and also by mating female C57BL/6 mice to male A/J mice. As shown in the notes associated with Table 2, the female parent is listed first, and since “A” is the accepted abbreviation for the A/J strain and “B” is the accepted abbreviation for the C57BL/6 strain, these breedings are depicted as “AXB” and “BXA”, respectively. Tables 2 and 3 then summarize the results of the backcross and intercross breedings and analyses, respectively.

For example, Table 2 of Howard shows the following backcrosses:  $(AXB)F_1 \times A/J$ , which generated 430  $F_2$  individuals, and  $A/J \times (AXB)F_1$ , which generated 42  $F_2$  individuals. Applicants respectfully submit that Table 2 also shows that there was an approximately 50:50 distribution of *ska/ska*  $F_2$  individuals to *ska/+*  $F_2$  individuals. This is what would have been predicted from a typical backcross of a trait that results from the segregation of a single autosomal recessive gene under this particular breeding strategy.

To elaborate, since A/J and C57BL/6 are both non-recombinant inbred strains, each animal of each strain is genetically identical and homozygous at every locus to every other member of the strain. A/J mice display the mammary gland patterning abnormalities, and thus are assumed to be *ska/ska* (*i.e.*, homozygous mutant at the *ska* locus). C57BL/6 mice do not display the mammary gland patterning abnormalities, and thus are assumed to be *+/+* (*i.e.*, homozygous wild type at the *ska* locus). The  $F_1$

animals will all be *ska*/+ (*ska* from the A/J parent and + from the C57BL/6 parent). Breeding a *ska*/+ F<sub>1</sub> individual to an A/J individual in a backcross would be expected to produce 50% *ska/ska* and 50% *ska*/+ F<sub>2</sub> individuals. The data shown in Table 2 display this frequency of phenotypes in the F<sub>2</sub>, indicating that the “backcrosses” that Howard discloses are typical backcrosses of F<sub>1</sub> individuals and not backcrosses of RI individuals. Applicants respectfully submit, however, that if the F<sub>1</sub> animals were produced by backcrossing RI individuals, the ratios seen in Table 2 would not have been observed.

As such, applicants respectfully submit that where Howard discloses on page 237 that they “are now mapping the *ska* gene in the AXB/BXA recombinant inbred strains of mice and in our backcross and intercross panels” (emphasis added), the “backcross and intercross panels” are the backcross and intercross mice discussed hereinabove (*i.e.*, the F<sub>2</sub> mice from Tables 2 and 3) and are not backcrosses or intercrosses of RI individuals. Therefore, applicants respectfully submit that the Patent Office’s assertion that Howard intercrossed or backcrossed RI individuals is believed to be based on an incorrect interpretation of the reference.

Accordingly, applicants respectfully submit that Howard does not anticipate instant independent claim 1 because Howard does not teach that the recombinant inbred lines AXB and BXA were backcrossed and intercrossed.

Additionally, applicants respectfully submit that the mapping populations that are disclosed in Howard (*i.e.*, the RI lines and the F<sub>2</sub> individuals from the backcross and intercross panels) do not constitute a renewable population of genetically diverse individuals as recited in claim 1. Applicants respectfully submit that it is clear that each member of the F<sub>2</sub> generation that is produced in a backcross or an intercross does not have a genome that can be regenerated as recited in claim 1 since meiotic recombination in the germ cells of the F<sub>1</sub> individuals would result in random rearrangements of the haploid genomes each parent passed onto the next generation cannot be regenerated. With respect to RI individuals, these are known to be homozygous at every locus, and thus cannot be heterozygous for a detectable polymorphism as also recited in claim 1. Therefore, applicants respectfully submit that



the intercross and backcross progeny referred to in Howard do not support the instant rejection of claim 1.

Applicants further respectfully submit that Howard does not anticipate instant claim 60 because Howard does not disclose a renewable population of genetically diverse individuals produced by crossing or backcrossing members of different recombinant inbred lines for one generation as recited in claim 60. Therefore, applicants respectfully submit that Howard does not anticipate claim 1 or claim 60.

Notwithstanding the above and in an effort to facilitate prosecution, applicants have amended claim 1 to recite *inter alia* that the renewable population of genetically diverse individuals comprises genetically diverse individuals selected from the group consisting of (a) individuals produced by crossing different recombinant inbred lines for one generation; (b) individuals produced by backcrossing recombinant inbred lines for one generation; (c) a cloned population of genetically diverse individuals; and (d) a panel of cell lines derived from genetically diverse individuals. Applicants respectfully submit that Howard does not disclose these elements.

Therefore, applicants respectfully submit that Howard does not disclose each and every element of claim 1 or of claim 60, and thus does not support a rejection under 35 U.S.C. § 102(a) of claims 1 and 60. Claim 2 has been canceled, and thus the instant rejection is believed to be moot as to claim 2. Claims 3-10 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished from Howard. Therefore, applicants respectfully request that the rejection of claims 1, 3-10, and 60 under 35 U.S.C. § 102(a) over Howard be withdrawn, and further that these claims are in condition for allowance. Applicants respectfully solicit a Notice of Allowance to that effect.

#### IV.B. The Rejection Over Diehl

Claims 1-10, 15, 19-27, 46-53, 64-74, 76, and 77 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Diehl. According to the Patent Office, Diehl discloses confirming their studies using both additional RI lines from the AXB and BXA set and backcross and intercross experiments. Thus, the Patent Office contends that even though Diehl may not have actually backcrossed or intercrossed the RI lines and

used them for mapping, Diehl suggests doing this and therefore anticipates the instantly claimed invention.

Applicants respectfully disagree. Applicants respectfully submit that contrary to the Patent Office's assertion, Diehl's disclosure that "[w]hile we view our findings as strongly supportive we believe that independent conformation is necessary via studies using both additional RI lines from the AXB and BXA set and backcross and intercross experiments" on page 5234 fails to support the instant rejection. Applicants respectfully submit that this assertion appears to be based on the Patent Office's contention that the "backcross and intercross experiments" refer to backcrosses and intercross of RI lines.

Rather, applicants respectfully submit that after review of Diehl one of ordinary skill in the art would understand that the "backcross and intercross experiments" referred to therein would be backcrosses and intercrosses of an F<sub>1</sub> generation produced by crossing an A/J individual to a C57BL/6 individual. As set forth hereinabove, these F<sub>2</sub> individuals cannot make up a renewable population of genetically diverse individuals, wherein each genetically diverse individual comprises a genome that can be regenerated. Therefore, applicants respectfully submit that Diehl does not support a rejection of claims 1 and 46 and dependent claims thereof, each of which includes this element.

Continuing with the instant rejection, independent claim 1 recites *inter alia* (a) providing a renewable population of genetically diverse individuals, wherein (i) each genetically diverse individual comprises a genome that can be regenerated; and (ii) one or more of the genetically diverse individuals are heterozygous for a detectable polymorphism. Applicants respectfully submit that the RI lines disclosed in Diehl do not comprise genetically diverse individuals that are heterozygous for a detectable polymorphism as recited in claim 1. Applicants respectfully submit that each member of an RI line is homozygous at every locus, and thus cannot be heterozygous for a detectable polymorphism. Therefore, individual members of the RI lines disclosed in Diehl do not anticipate claim 1 or dependent claims thereof.

Furthermore, applicants respectfully submit that independent claims 46 and 74 also recite these distinguishing elements. Therefore, applicants respectfully submit that

claims 46 and 74, and dependent claims thereof, are also believed to be distinguished over Diehl.

Applicants further respectfully submit that claim 64 recites *inter alia* providing a renewable population of genetically diverse individuals comprising a panel of cell lines derived from genetically diverse individuals, wherein the cell lines are animal cell lines each of which comprises a genome that can be regenerated. Applicants respectfully submit that Diehl does not disclose any cell lines, and thus cannot be read to anticipate claim 64 and dependent claims thereof.

Accordingly, applicants respectfully submit that Diehl does not teach each and every element of independent claims 1, 46, 64, and 74, and thus does not support a rejection of these claims under 35 U.S.C. § 102(b). Applicants further respectfully submit that each of claims 2-10, 15, 19-27, 47-53, 65-73, 76, and 77 depends from one of distinguished claims 1, 46, 64, or 74, and thus are also believed to be distinguished over Diehl. Claims 2 and 47 have been canceled, and thus the instant rejection is believed to be moot as to these claims. Thus, applicants respectfully submit that claims 1, 3-10, 15, 19-27, 46, 48-53, 64-74, 76, and 77 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

#### V. Response to the Obviousness Rejection

Claims 11-14, 16-18, and 61-63 have been rejected under 35 U.S.C. § 103(a) as being obvious over Diehl in view of Dindzans, and further in view of Hedrich. According to the Patent Office, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates a phenotype method of Diehl so as to have included the diverse population of non-recombinant, parent lines of Dindzans and to have derived their breeding population from at least 3, 4, or 8 non-recombinant parent lines as taught in further view of Hedrich, not only for the expected benefit that more parents would obviously result in a more diverse progeny, but also for the expected benefit of providing an additional means for furthered variation among mouse lines and for the ability taught by Hedrich of making "it possible to select among the lines that one which matches the original standards best".

After careful consideration of the rejection and the Patent Office's bases therefore, applicants respectfully traverse the rejection and submit the following remarks.

Initially, applicants respectfully note that this rejection has been maintained from the previous Official Action, and that the Patent Office did not find applicants' remarks presented in response to the previous rejection persuasive. The Patent Office asserted the following in its Response to Arguments with respect to the maintained rejection follows:

With regard to the rejections over Diehl in view of Dindzans and in further view of Hedrich the Applicants argued that the combined references do not teach each and every element of the claims, and further that this combination in fact teaches against the subject matter recited in the claims. With regard to Diehl applicants state that only inbred individuals that are homozygous at every locus are disclosed. This argument has been addressed above. Although Diehl may not have actually backcrossed or intercrossed the RI lines and used them for mapping, Diehl suggests doing this and therefore anticipates the instantly claimed invention. With regard to Dindzans applicants state that Dindzans does not teach or suggest the use of heterozygous mice and in fact teaches against the use of such mice. The examiner agrees that this statement is true. The Dindzans reference is only being relied upon to teach how the RI lines were derived, therefore Dindzans is not required to teach a genetically diverse population. With regard to Hedrich applicants state that this reference also teaches the creation of mice that are homozygous at every locus. The examiner agrees that this statement is true. The Hedrich reference is only being relied upon to teach how the RI lines were derived, therefore Hedrich is not required to teach a genetically diverse population. Thus the combination of these references teach how to develop RI lines useful for mapping and Diehl further suggests intercrossing and backcrossing the RI lines to confirm which loci are involved in clefting. For these reasons the rejections over Diehl in view of Dindzans and in further view of Hedrich are maintained.

June 2007 Final Official Action at page 13 (emphases added).

Initially, applicants respectfully disagree with several of these assertions. First, applicants respectfully submit that with respect to the assertion that "[a]lthough Diehl may not have actually backcrossed or intercrossed the RI lines and used them for mapping, Diehl suggests doing this and therefore anticipates the instantly claimed invention", applicants have addressed this assertion hereinabove with respect to the

anticipation rejection over Diehl. Summarily, applicants respectfully submit that the Patent Office's assertion that Diehl suggests backcrossing or intercrossing RI lines represents an incorrect interpretation of Diehl. As set forth hereinabove, the individuals backcrossed or intercrossed in Diehl are  $F_1$  individuals and not RI individuals.

Thus, applicants respectfully submit that contrary to the Patent Office's assertion, Diehl does not disclose or suggest the subject matter of claim 60, which recites *inter alia* a renewable population of genetically diverse individuals comprising individuals produced by crossing or backcrossing members of different RI lines for one generation. Additionally, applicants respectfully submit that with respect to claim 1, since backcrossing or intercrossing  $F_1$  individuals as suggested in Diehl does not allow for the creation of genetically diverse individuals comprising a genome that can be regenerated as recited in claim 1, applicants respectfully submit that also contrary to the Patent Office's assertion, Diehl does not anticipate claim 1.

Second, the Patent Office asserts that both Dindzans and Hedrich are "only being relied upon to teach how the RI lines were derived". With respect to this assertion, applicants respectfully submit that in the Materials and Methods section beginning on page 2355, Dindzans simply discloses what is a well known procedure for generating RI lines: namely, crossing two non-recombinant inbred lines (C57BL/6J and A/J) to produce an  $F_1$ , intercrossing the  $F_1$  to generate a plurality of  $F_2$  individuals, and inbreeding the  $F_2$  individuals for more than 20 generations (in the case of Dindzans, more than 30 generations) to generate a plurality of RI lines. To generate the various AXB RI lines, the initial breeding involved an A/J female and a C57BL/6J male, and to generate the various BXA RI lines, the initial breeding involved a C57BL/6J female and an A/J male.

Further, it is believed that this is how the AXB and BXA RI lines disclosed in Diehl would have been generated. Therefore, with respect to the basis upon which the Patent Office relies on Dindzans, applicants respectfully submit that Dindzans adds no more than what one of ordinary skill in the art would have understood from Diehl: *i.e.*, that AXB and BXA RI lines were employed, and how these lines would have been generated.

Turning now to Hedrich, applicants respectfully submit that Hedrich does not relate in any manner to RI lines, and thus the Patent Office's assertion that Hedrich is "only being relied upon to teach how the RI lines were derived" finds no support in the reference itself. Rather, Hedrich teaches techniques that can be employed for the propagation (*i.e.*, the maintenance, and not the generation of) of an inbred strain to ensure the genetic identity of its members with other members of the strain. This does not teach how to generate a recombinant inbred strain. As such, applicants respectfully submit that the basis on which the Patent Office has stated it is relying on Hedrich is not present within the disclosure of Hedrich. There is no disclosure or teaching in Hedrich regarding how RI lines are derived.

Third, the Patent Office asserts that "the combination of these references teach how to develop RI lines useful for mapping and Diehl further suggests intercrossing and backcrossing the RI lines to confirm which loci are involved in clefing". As set forth in the applicants' remarks immediately hereinabove, this assertion by the Patent Office is believed to be incorrect.

Continuing with the instant rejection, the Patent Office contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the identification of a genetic locus that modulates a phenotype method of Diehl so as to have included the diverse population of non-recombinant, parent lines of Dindzans and to have derived their breeding population from at least 3, 4, or 8 non-recombinant parent lines as taught in further view of Hedrich, not only for the expected benefit that more parents would obviously result in a more diverse progeny, but also for the expected benefit of providing an additional means for furthered variation among mouse lines and for the ability taught by Hedrich of making "it possible to select among the lines that one which matches the original standards best". Applicants respectfully submit that this assertion is also unsupported by the cited references.

Applicants respectfully submit that this assertion appears to suggest that Dindzans teaches a diverse population of non-recombinant, parent lines. However, applicants respectfully submit that Dindzans, like Diehl, only employed two non-recombinant parent lines: A/J and C57BL/6J. Applicants respectfully submit that since at

least two parent lines (generally non-recombinant inbred lines like A/J and C57BL/6J) must be employed to generate a series of RI lines, applicants respectfully submit that Dindzans again teaches nothing with respect to the use of non-recombinant parent lines that one of ordinary skill in the art would not have recognized from Diehl.

Turning now to the disclosure of Hedrich, applicants respectfully submit contrary to the Patent Office's assertion, that there is no disclosure in Hedrich that can be interpreted as encompassing at least 3, 4, or 8 non-recombinant parent lines. Applicants respectfully submit that the 8-10 breeding pairs disclosed in Hedrich are all members of the same inbred mouse line, and that these mice are employed for the purpose of propagating (i.e., no generating) an inbred strain by deleting genetic variation that has arisen in the strain. Applicants respectfully submit that the phrase "the one which matches the original standards best" refers to the member of the 8-10 breeding pairs that is most identical to the "original standard" (i.e., the exemplary member of the inbred strain). Employing this member as the new founder of the strain removes to the greatest extent possible any genetic variation that as shown up in the various members of the breeding pairs.

Therefore, applicants respectfully submit that like Diehl and Dindzans, Hedrich does not teach ways of increasing genetic diversity, but of decreasing it. In each case, applicants respectfully submit that the references are concerned with generating and propagating inbred lines.

Summarily, applicants respectfully submit that the Patent Office's assertion that any of Diehl, Dindzans, or Hedrich would motivate one of ordinary skill in the art to generate renewable populations of genetically diverse individuals that are heterozygous for a detectable polymorphism as set forth in claim 1 is based on an incorrect interpretation of these references. Applicants further respectfully submit that each of these references teaches techniques for generating and/or propagating inbred lines, which is believed to actually teach away from generating the populations recited in the instant claims.

Accordingly, applicants respectfully submit that the combination of Diehl, Dindzans, and Hedrich do not support a rejection of claims 11-14, 16-18, and 61-63

under 35 U.S.C. § 103(a). Applicants respectfully request that the instant rejection be withdrawn, and further that the instant claims be allowed at this time.

### CONCLUSIONS

In light of the above amendments and remarks, applicants submit that the application is in condition for allowance and courteously solicit a Notice of Allowance.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

### DEPOSIT ACCOUNT

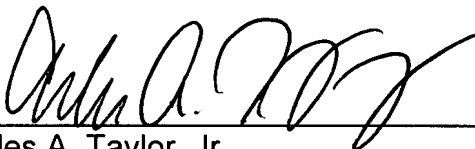
The Commissioner is hereby authorized to charge any deficiencies of payment or credit any overpayments associated with the filing of this correspondence to Deposit Account No. 50-0426.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: October 31, 2007

By: \_\_\_\_\_



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